REMARKS

This responds to the Office Action dated April 29, 2010.

Claims 173, 182, 200, and 231 are amended. Claims 173-194, 196-200, 202-203, 205-206, 231, and 234 are pending.

The Non-Statutory Obviousness-Type Double Patenting Rejections

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153-173 of copending application Serial No. 10/729,056. As previously noted, since neither the present application nor the ′056 application has been allowed, no terminal disclaimer is required at this time. Should a terminal disclaimer be required, the Office may request it upon a notice of allowable subject matter in either the present application or the ′056 application.

Claims 200, 202-203 and 205-206 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,410,587 B1 in view of Grainger et al. (WO 94/26303). This rejection is respectfully traversed.

The Examiner failed to respond to Applicant's arguments in the response filed on February 12, 2010 that claims 200, 202-203 and 205-206 are patentably distinct relative to claim 8 of U.S. Patent No. 6,410,587 in view of Grainger et al. (WO 94/26303), as required by M.P.E.P. 821.01.

Claim 8 in the ′587 patent is directed to a therapeutic method for lowering serum cholesterol comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula VI.

The present claims at issue differ by at least the population to be treated, the agents employed in the methods, and/or the outcome to be achieved. For example, note that none of droloxifene, toremifene, idoxifene, or raloxifene, all recognized as tamoxifen analogs, fall within the scope of formula VI in claim 8 of the ‘587 patent. Moreover, the agents recited in claim 8 of the ′587 patent do not necessarily elevate TGF-beta levels, e.g., active TGF-beta1 levels. In this

regard, the Examiner is requested to consider that not all structural analogs of tamoxifen elevate TGF-beta (see the Rule 132 Declaration filed on August 12, 2009 in copending application Serial No. 10/729,056; copy enclosed herewith), and not all agents that elevate active TGF-beta elevate latent TGF-beta (see, e.g., the '587 patent). Further, serum cholesterol includes both VLDL, LDL and HDL cholesterol. An agent that lowers LDL does not necessarily alter HDL cholesterol (see the abstract for Castro et al., Mayo Clin. Proc., 74:1125 (1999); tamoxifen lowers total and LDL cholesterol and increases HDL cholesterol; Smith et al., J. Clin, Oncol., 26:1824 (2008); toremifene increases LDL but has no significant impact on HDL; and the abstract for Mulder et al., Eur. Heart J., 19: 237 (1998), which disclose that 5-10 mg of idoxifene decreases LDL and HDL cholesterol levels).

Thus, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '587 patent and Grainger et al. is respectfully requested.

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 5,847,007 of record in view of Chander et al. (Cancer Res., 51:5851 (1991)). This rejection is respectfully traversed.

The Examiner failed to respond to Applicant's arguments in the response filed on February 12, 2010 that claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 are patentably distinct relative to claims 1-16 of U.S. Patent No. 5,847,007 of record in view of Chander et al., as required by M.P.E.P. 821.01.

The present claims at issue differ from those in the '007 patent by at least the route of administration, population to be treated, agents employed, and/or the outcome to be achieved. For instance, the claims in the '007 patent are directed to methods in which an amount of an agent is orally administered to elevate TGF-beta levels so as to inhibit atherosclerotic lesion formation or development in a mammal or stabilize atherosclerotic plaque, inhibit lipid accumulation, or inhibit or reduces diminution in vessel lumen diameter in a diseased vessel. In contrast, claim 173 is directed to a method in which a cytostatic amount of compound of formula (I) is locally administered to a human with a cardiovascular indication; claim 182 is directed to a method in which a compound of formula (I) is administered to a diabetic mammal with a

cardiovascular indication; claim 200 is directed to a method of increasing the level of TGF-beta in a human identified as being afflicted with a cardiovascular indication characterized by a decreased lumen vessel diameter, comprising selecting an agent that is structural analog of tamoxifen or a pharmaceutically acceptable salt thereof that directly or indirectly elevates the level of active TGF-beta1 in a human and administering to a human identified as being afflicted with a cardiovascular indication an effective amount of the agent; and claim 231 is directed to a method in which a compound of formula (I) is employed to treat a mammal having vascular insufficiency in the limbs, peripheral neuropathy or retinopathy.

Therefore, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '007 patent and Chander et al. is respectfully requested.

The Rejections of Claims Under § 103

Claims 173-175, 177, 179-181, 196-200, 203, 205-206, and 231 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 44:357 (1992)). This rejection is respectfully traversed.

In the Response to Arguments section of the Office Action, which responds to statements in a Rule 132 Declaration executed by Dr. David Grainger, one of the co-inventors named on the present application, the Examiner asserts that the fact that toremifene has estrogenic activity and is used to treat breast cancer does not change its effect of reducing serum cholesterol which is disclosed in Sawada et al.

The Sawada et al. article is focused on determining the toxicity of toremifene, which is of interest to Sawada et al. since toremifene is expected to be used in the treatment of breast cancer (page 1 of the translation). Moreover, Sawada et al. were focused on the anti-estrogenic activity of toremifene. See pages 1 and 13 of the translated Sawada et al. article: "[b]ecause the use of this drug is to be limited to female patients, only female rats were tested" (page 1 of translation); and that the decreases observed in total cholesterol (T-Chol) and phospholipids (PL) after toremifene administration were "believed to be caused by lipid synthesis inhibition related to the anti-estrogen effect" (page 13 of the translation). Clearly cardiovascular and vascular indications and aberrant cholesterol levels are not associated with a single gender, although breast cancer is

highly gender specific. And even if Sawada et al. observed a decrease in cholesterol levels, Sawada et al. did not comment on any uses for toremifene other than for breast cancer.

The Examiner failed to address the fact that an agent that lowers total cholesterol does not indicate that the same agent would in any way be beneficial in lowering LDL cholesterol, much less indicate that the agent would be beneficial in preventing or inhibiting heart disease. See, e.g., the abstract for Castro et al., Mayo Clin. Proc., 74:1125 (1999), which disclose that tamoxifen lowers total and LDL cholesterol and increases HDL cholesterol; Smith et al., J. Clin, Oncol., 26:1824 (2008), which disclose that toremifene decreases LDL and increases HDL, but the latter is reported as 0.5% ± 2.2%; the abstract for Agnusdei et al., Ann. Endocrinol., 60:242 (1999), which disclose that raloxifene decreases total serum and LDL cholesterol but did not significantly vary HDL cholesterol; and Okubo et al., Kidney Intl., 56: S229 (1999), which disclose that probucol (another lipid lowering drug) lowers both LDL and HDL cholesterol but not VLDL cholesterol (a copy of each is enclosed).

In this regard, please consider that decreases in cholesterol in agent treated animals may be indicative of toxicity and not necessarily that the agent would be useful to therapeutically lower cholesterol or provide a cardiovascular benefit (see, e.g., the abstract for Kockaya et al., Drug Chem. Toxicol., epub June 16 2010, which discloses that a drug intended for pain and inflammation decreased cholesterol; and an abstract entitled "Toxicity Studies of 1,3-Diphenylguanidine (CAS No. 102-06-7) Administered in Feed to F344/N Rats and B6C3F1 Mice," which discloses that 1,3-diphenylguanidine, an accelerator in the vulcanization of rubber, lowers serum protein, cholesterol, triglyceride, and creatine concentrations) (a copy of each is enclosed).

Also in the Response to Arguments section of the Office Action, the Examiner alleges that the mechanism of action of an antiestrogen increasing TGF-beta was known (Grainger et al.; WO 94/26303) and so it would have been obvious to one of ordinary skill in the art to employ tamoxifen analogs to treat atherosclerosis to achieve the expected benefit of lowering cholesterol.

However, the Examiner failed to respond to Dr. Grainger's statement that it was surprising that compounds within the scope of the claims would be useful to inhibit or treat a variety of cardiovascular or vascular indications, since the presence of anti-estrogenic activity in

a sub-group of the compounds would not have predicted this. That is because, as of the effective filing date of the present application, Dr. Grainger states that anti-estrogens would have been expected, if anything, to exacerbate the risk of cardiovascular disease (estrogen was believed to be cardioprotective). Since estrogen was believed to be cardioprotective and toremifene was an anti-estrogen (see the abstract for Sawada et al.), the administration of an anti-estrogen to females would counteract the protective effects of estrogen in normal animals. In contrast, diseases such as breast cancer that were linked to the estrogen receptor, were believed to be amenable to treatment by anti-estrogens.

In addition in the Response to Arguments section of the Office Action, the Examiner alleges there is a reasonable expectation of success in treating atherosclerosis, a condition in which fatty materials collect along the walls of the arteries, since lowering the total amount of cholesterol in the artery would be expected to lower fatty material buildup in the walls of the arteries.

Applicant respectfully disagrees. As noted in Kullo et al. (Mayo Clin. Proceed., 80:219 (2005)) (copy enclosed), although most patients who experience a coronary heart disease (CHD) event have one or more of the conventional risk factors for atherosclerosis, so do many people who have not yet experienced such an event. Therefore, the fact that Sawada et al. report that toremifene administration to normal female rats reduced total cholesterol levels does not provide a reasonable expectation that toremifene is useful to treat atherosclerosis.

Withdrawal of the § 103 rejection over Sawada et al. is respectfully requested.

Claims 173-177, 179-194, 196-199, and 205-206 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang (U.S. Patent No. 5,445,941). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

The Examiner, in the Response to Arguments section of the Office Action, asserts that the subject population in Yang that suffer from osteoporosis are at risk of developing coronary artery disease, atherosclerosis and myocardial infarction, as taught by Yang, and so it would be obvious to treat that population with an anti-estrogen.

Human fetal fibroblasts have no apparent relationship to osteoporosis (bone loss) or any particular cardiovascular or vascular disorder. Therefore, there is no logical connection between the disclosure in Yang that toremifene induces TGF-beta secretion from human fetal fibroblasts in the absence of estrogen receptor expression and the use of toremifene to treat a cardiovascular condition or a diabetic mammal.

Accordingly, withdrawal of the § 103 rejection over Yang is respectfully requested.

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Grainger et al. (WO 94/26303) of record in view of Chander et al. This rejection is respectfully traversed.

In the Response to Arguments section of the Office Action, the Examiner alleges that although the Grainger Declaration states that it was surprising that compounds within the scope of the claims in the present application would be useful to inhibit or treat a variety of cardiovascular or vascular indications, as they would have been expected to act as anti-estrogens and that would have been expected to exacerbate the risk of cardiovascular disease, that was not persuasive. The Examiner explains that is because at the time of the invention, it was known that tamoxifen or toremifene induce the secretion of TGF-beta which is an important inhibitor of revascularization, which causes the pathogenesis of diabetic retinopathy as taught by Yang and Frank.

First, the rejection over the Grainger et al. document is over the combination of Grainger et al. and Chander et al., not Grainger et al., Yang and Frank et al. Second, the Examiner has failed to set forth facts and reasoning why Dr. Grainger's statements related to the surprising properties of compounds within the scope of the claims in view of the state of the art as of the effective filing date of the present application is not sufficient to overcome the § 103 rejection over Grainger et al. and Chander et al. For example, Dr. Grainger points out that raloxifene, which has anti-estrogenic properties and has some structural similarities to tamoxifen, does not elevate TGF-beta1 levels. Therefore, all tamoxifen analogs are not alike.

Therefore, withdrawal of the § 103 rejection over Grainger et al. and Chander et al. is respectfully requested

Claims 231 and 234 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang in view of Frank (Ophthalmology, 98:586 (1991)). This rejection is respectfully traversed.

The abstract for Frank discloses that several growth factors in the retina may promote neovascularization, e.g., acidic and basic fibroblast growth factor, and that TGF-beta produced by capillary pericytes and smooth muscle cells may inhibit neovascularization. The abstract does not disclose or suggest any relationship between any specific growth factor and diabetic retinopathy. Moreover, neither Yang nor Frank et al. teach or suggest the use of compounds of formula (I) to treat vascular insufficiency in the limbs, peripheral neuropathy or retinopathy. Therefore, there is no logical connection between the disclosure in Yang that toremifene induces TGF-beta secretion from human fetal fibroblasts in the absence of estrogen receptor expression and the disclosure in Frank, and Applicant' method.

Hence, withdrawal of the § 103 rejection over Yang and Frank is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone the undersigned at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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Date August 17, 2010

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 17th day of August, 2010.

DAWN M. POOLE

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Signature